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Chlordimeform Produces Contrast-Dependent Changes in Visual Evoked Potentials of Hooded Rats

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16. ABSTRACT

Acute exposure to the insecticide/acaricide chlordimeform (CDM) produces large, selective and transient changes in visual evoked potentials of rats. Experiments were conducted investigating the influence of physical characteristics of the evoking stimuli on the CDM effect. Adult male Long-Evans rats with epidural visual cortex electrodes were used. In Experiment 1, several alternating square wave grating pattern sizes were used to elicit pattern reversal evoked potentials (PREPs). In Experiment 2, PREPs were elicited with gratings oriented at 0 (horizontal), 45°, 90°, or 135°. Treatment with 40 mg/kg CDM increased PREP amplitudes and latencies regardless of orientation. In Experiment 3, flash evoked potentials (FEPs), elicited with strobe flashes spanning four log units of intensity, showed a small but significant CDM dose X intensity interaction on P2N2 peak-to-peak amplitude. In Experiment 4, PREPs were elicited withalternating gratings having s sinusoidal spatial luminance profile and variable spatial frequency (0.2 or 0.8 cpd) and contrast (threshold to 65%). Rats treated with 40 mg/kg CDM showed increased peak-to-peak amplitudes only at 0.2 cpd and only at contrast values above 10%. The results suggested selective action of CDM on visual motion detection mechanisms.

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Chlordimeform Produces Contrast-Dependent Changes in Visual Evoked Potentials of Hooded Rats

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Previous experiments found that acute exposure to the insecticide/acaricide, chlordimeform (CDM), produced large increases in the amplitude of pattern reversal evoked potentials (PREPs) without changing the amplitude of flash evoked potentials (FEPs) in the same rats (W. K. Boyes and R. S. Dyer, *Exp. Neurol.* **86:** 434–447, 1984). Current work investigated the influence of physical characteristics of the evoking stimuli on the action of CDM. Adult male Long–Evans rats with epidural visual cortex electrodes were used. In experiment 1, PREPs were elicited with alternating gratings having equal contrast (99%) and a square wave spatial luminance profile at several spatial frequencies. Rats treated 1 h previously with 40 mg/kg CDM had increased PREP amplitudes at 0.1, 0.2, and 0.4 cycles per degree (cpd), but not at 0.8 cpd. No changes were found after 5 mg/kg CDM. In experiment 2, PREPs were elicited with gratings oriented at 0° (horizontal), 45°, 90°, or 135°. Treatment with 40 mg/kg CDM increased PREP amplitudes and latencies regardless of orientation. In experiment 3, FEPs elicited with strobe flashes spanning four log units of intensity showed a small but significant CDM dose × intensity interaction on P2N2 peak-to-peak amplitude. In experiment 4, PREPs were elicited with alternating gratings having a sinusoidal spatial luminance profile, spatial frequency of 0.2 or 0.8 cpd, and contrast ranging from noise levels to 65%. Rats treated with

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Abbreviations: CDM—chlordimeform; FEP, PREP—flash, pattern reversal evoked potential, cpd—cycles per degree.

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40 mg/kg CDM showed increased peak-to-peak amplitudes only at 0.2 cpd and only at contrast values above 10%. The failure of CDM to alter PREPs at 0.8 cpd was attributed to low contrast sensitivity at that spatial frequency. The results demonstrated that the action of CDM on visual evoked potentials was dependent on the amount of contrast in the stimulus pattern, and suggested that CDM alters the encoding of visual contrast. © 1985 Academic Press, Inc.

INTRODUCTION

Chlordimeform (CDM) is a formamidine insecticide/acaricide with a wide spectrum of biological actions (19, 25, 28), but little is known about its effects on the function of intact mammalian nervous systems. Recently, acute exposure to CDM was found to produce large but transient increases in the amplitude of pattern reversal evoked potentials (PREPs) of hooded rats without changing the amplitude of flash evoked potentials (FEPs) (6). The enhancement of PREP but not FEP amplitude indicated that CDM had selective actions on mammalian visual function related, in some fashion, to the properties of visual stimuli.

The stimuli used previously to elicit PREPs and FEPs were quite different. The PREP-eliciting stimulus was a series of abruptly reversing black and white horizontal bars. The PREP stimulus was a high-contrast pattern, of a specific size and orientation, and a constant overall illumination level. The FEP-eliciting stimulus was a brief, bright strobe-lamp flash, devoid of pattern, orientation and contrast, and presented against a very different level of adapting illumination. Features such as pattern size, orientation, contrast, and illumination are important determinants of the response of visual neurons. Because CDM showed selective actions on visual evoked potentials which differed along these parameters, a series of experiments was conducted to explore the dependence of CDM action on parametric manipulations of the physical characteristics of the eliciting stimuli.

EXPERIMENT 1

Materials and Methods

The influence of the primary spatial frequency of the eliciting stimulus pattern on CDM action was examined. Beginning with the report of Campbell and Robson (11), a variety of evidence indicates that visual processes are divided into spatial-frequency selective channels. Spatial frequency channels may be differentially altered in human visual disorders (35). Refractive errors may diminish high spatial-frequency sensitivity and result in a loss of visual acuity. Occasionally, patients with neurologic disorders demonstrate selective deficits in the middle or low ranges of spatial frequency (2, 3). The primary spatial frequency power of a grating

with a square wave luminance profile, such as the black-and-white bar stimulus used previously to elicit PREPs (6), can be changed by simply changing the width of the bars on the screen.

For the most part, the experimental procedures were identical to those described elsewhere (5, 6). Briefly, adult male Long–Evans hooded rats (Charles River) weighing 250 to 400 g were used. Chronic epidural stainless-steel electrodes were surgically implanted under Chloropent anesthesia at least 1 week prior to testing. For each rat the active recording electrode was placed over visual cortex 6 mm posterior to bregma and 4 mm lateral to midline, and reference and ground electrodes were placed 2 mm anterior to bregma and 2 mm to the right and left of midline, respectively.

Dosage. Chlordimeform HCl (97% pure from NOR-AM Agricultural Products, Naperville, Ill.), was dissolved in isotonic saline and administered in single i.p. injections in a volume of 1 ml/kg body weight 1 h before testing; doses were 0 (saline, $N = 12$), 5 ($N = 12$), and 40 ($N = 13$) mg/kg CDM HCl, measured as the salt.

The PREPs were recorded from awake, harness-restrained rats placed in front of the television screen of a Grass Model VPG pattern generator. Pupils were not dilated. The eliciting stimulus was a black-and-white square-wave grating (99% contrast, 30 cd/m^2, $51° \times 58°$ field size) which had primary spatial frequency power at 0.1, 0.2, 0.4, or 0.8 cycles per degree visual angle (cpd). The gratings were temporally modulated as a square wave (i.e., the black and white bars abruptly reversed position with no overall change in mean luminance). Evoked responses were triggered at every pattern shift at 0.5 Hz, and 200 trials were averaged. In addition, 200 trials of random electrocortical activity (no eliciting stimulus) were averaged for an estimate of the recording noise level. The pattern size and noise conditions were presented in a counterbalanced order.

Electrocortical activity was amplified, filtered, A/D converted, and computer averaged using described procedures (5, 6). Group-averaged evoked potential waveforms were computed from the stored average obtained from each rat, and are presented here to illustrate group trends. All statistical analyses, however, were carried out on the individual rat values. Statistical procedures followed the guidelines of Muller *et al.* (29).

Results

Both stimulus size and CDM exposure had strong influences on PREP waveforms in experiment 1. Group-averaged waveforms for all three dose groups at all pattern sizes plus the averaged noise level are presented in Fig. 1. With increasing primary spatial frequency, diminished peak amplitudes were evident. In the control and 5-mg/kg groups, component N2P2 was small at low spatial frequencies and undetectable at high spatial frequencies.

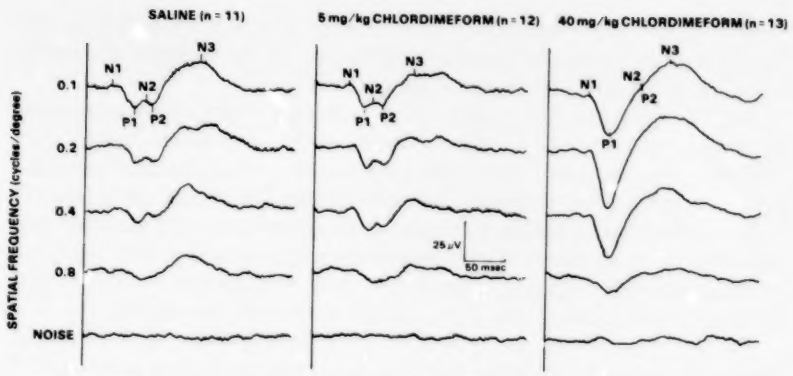


FIG. 1. Pattern reversal evoked potentials (PREPs) averaged for groups of rats treated with either saline or two doses of chlordimeform (CDM). Stimuli were high contrast (99%) square-wave gratings. Each rat received only one dose and all pattern sizes in a counterbalanced order. All groups showed diminished amplitudes and altered latencies with increasing stimulus primary spatial frequency. Waveforms at 0.8 cycles per degree (cpd), though small, were distinguishable from noise levels. Treatment with 40 mg/kg markedly increased PREP amplitude at 0.1, 0.2, and 0.4 cpd, but not at 0.8 cpd.

In the 40-mg/kg group, N2P2 was absent at all pattern sizes. The 5-mg/kg group was not obviously different from controls. The most evident effect of 40 mg/kg CDM was a large increase in P1 amplitude at 0.1 to 0.4 cpd. At 0.8 cpd, however the group-average waveform of 40 mg/kg appeared to be no larger than that of other groups. The effect of CDM exposure on PREP amplitudes as a function of pattern size is shown in Fig. 2. The N1P1 and P1N3 mean peak-to-peak amplitudes of the 40-mg/kg group were greater than those of controls for pattern sizes of 0.10, 0.20, and 0.40 cpd. At 0.80 cpd, however, the treated groups were not different from controls. The PREP amplitude MANOVA showed significant main effects of dose ($F(4,64) = 12.48$, $P < 0.0001$) and pattern size ($F(6,198) = 20.43$, $P < 0.0001$), and a significant dose × pattern size interaction ($F(12,198) = 5.31$, $P = 0.0001$). Both N1P1 and P1N3 amplitudes showed significant dose × pattern size effects (both Fs$(6,101) > 7.73$, both Ps < 0.0001). Tukey's test indicated that all peak amplitude differences were attributable to the 40-mg/kg group. In no case were the amplitudes of the 5-mg/kg group significantly different from controls. The 40-mg/kg group was significantly different from controls at 0.1, 0.2, and 0.4 cpd for N1P1, and at 0.2 and 0.4 cpd for P1N3. Neither amplitude measure was statistically different from controls at 0.8 cpd.

The latency of PREP peaks was influenced by both CDM exposure ($F(6,62) = 6.80$, $P < 0.0001$) and pattern size ($F(9,293) = 3.00$, $P = 0.0020$).

According to Tukey's test, the 40- but not the 5-mg/kg group was significantly different from controls. In general, the latency of PREP peaks was increased by 40 mg/kg CDM. Although in Fig. 2 some peak latencies appear to have been differentially changed by CDM at some spatial frequencies, these effects can not be assured because the PREP latency MANOVA showed a nonsignificant dose × pattern size interaction ($F(18,293) = 1.37$, $P = 0.1473$).

EXPERIMENT 2

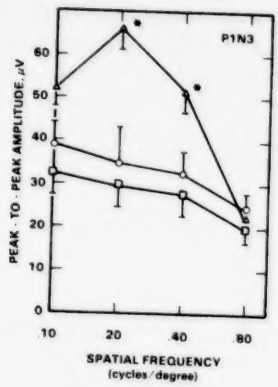
Materials and Methods

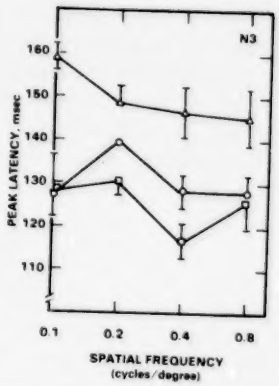
Experiment 1 showed that CDM altered PREPs in a manner dependent on the size of the eliciting stimulus, but only horizontally oriented stimuli were tested. Some visual system neurons respond differentially to stimulus orientation. Orientation specificity may be altered under certain conditions such as restricted visual experience during development (17). In addition, some patients with multiple sclerosis show orientation-specific visual deficits (10, 36).

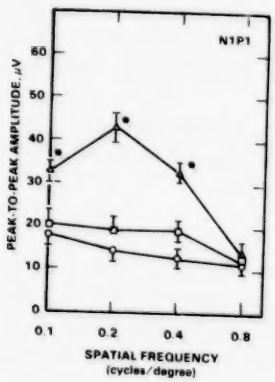
The influence of PREP stimulus orientation on the effect of CDM was studied by recording PREPs to four grating orientations, either 0° (horizontal), 45°, 90°, or 135°, achieved by rotation of the television set. Primary spatial frequency was 0.2 cpd. To assure a uniform field size across orientations, a circular black annulus was attached to the front of the television screen resulting in a field of 69° diameter. The orientation presentation order was counterbalanced. Rats received either 0 ($N = 13$) or 40 ($N = 14$) mg/kg CDM 1 h before testing. Because of previous negative results, 5 mg/kg was not tested; otherwise the methods were identical to those of experiment 1.

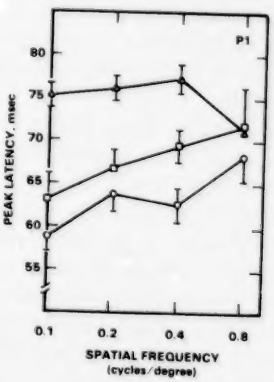
Results

The PREP amplitudes were not influenced by stimulus orientation; PREP peak-to-peak amplitudes and peak P1 and N3 latencies from experiment 2 are shown as a function of orientation and dose in Fig. 3. Amplitudes N1P1 and P1N3 were increased by CDM to approximately 300% of controls at all stimulus orientations. The MANOVA for PREP amplitudes indicated a significant dose effect ($F(2,24) = 32.53$, $P < 0.0001$), but the orientation effect ($F(6,146) = 2.20$, $P = 0.0465$) and the dose × orientation interaction ($F(6,146) = 0.85$, $P = 0.5317$) were not statistically significant. The PREP latencies were increased at all stimulus orientations by CDM ($F(3,23) = 16.95$, $P < 0.0001$). The orientation of the stimulus grating had a significant effect on PREP latencies (MANOVA $F(9,215) = 3.19$, $P = 0.0013$). This was attributable to N3 latency which was longer

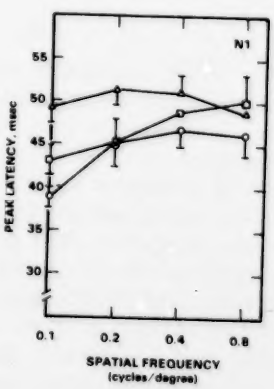








△ 40 mg/kg CHLORDIMEFORM (n = 13)
□ 5 mg/kg CHLORDIMEFORM (n = 12)
○ SALINE (n = 11)



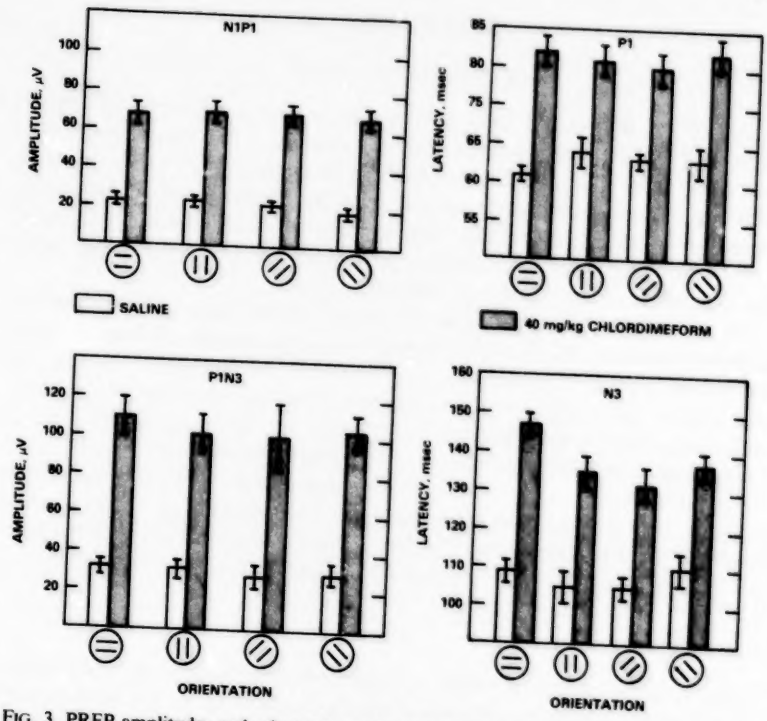


FIG. 3. PREP amplitudes and selected latencies as a function of pattern orientation in rats treated with either saline or CDM. Both peak-to-peak amplitudes and peak latencies were increased by CDM independent of stimulus orientation. Orientation had a small influence on N3 latency which was independent of dose.

with horizontal bars than with the other orientations ($F(3,75) = 7.99$, $P < 0.0001$). Although in Fig. 3 the N3 latency for horizontal bars appeared to be increased more for the CDM than the control group above the other orientations, this appearance was not supported statistically, as the dose × orientation MANOVA was not significant ($F(9,215) = 1.28$, $P = 0.2509$).

FIG. 2. PREP peak-to-peak amplitudes and peak latencies as a function of primary spatial frequency in rats treated with either saline, 5, or 40 mg/kg CDM. PREP amplitudes N1P1 and P1N3 were enhanced by 40 mg/kg CDM at the low and middle range spatial frequencies, but not at the high value of 0.8 cpd. All PREP peak latencies were increased by 40 mg/kg CDM, but not by 5 mg/kg CDM. That the CDM-induced latency increases were dependent on spatial frequency was not statistically supportable. In this and subsequent figures, the plotted values represent $\bar{x} \pm$ SEM.

EXPERIMENT 3

Materials and Methods

Experiment 3 Protocol. One possible reason for the failure of CDM to affect FEP amplitudes concerns stimulus intensity. The FEP stimuli used previously were elicited with the brightest stimulus available (6). Although FEP amplitudes using such stimuli can be increased with treatments including anesthesia combined with hypothermia (12), the supramaximal stimuli employed may have masked an increase in FEP amplitudes under the conditions of the CDM experiment.

To investigate the dependence of the CDM-induced FEP changes on stimulus intensity, FEPs were recorded to strobe flashes of four different intensities. The four intensities were achieved by harness-restraining the rats, placing them with their eyes either 4 or 48 cm from the strobe lamp, and setting the Grass stimulator at intensity selections of either 1 or 16. Thus, flash intensities calculated to be approximately 1.32×10^4, 2.85×10^5, 1.91×10^6, and 4.11×10^7 lx peak power were obtained. Each intensity was presented to every rat in a counterbalanced order. Evoked responses were averaged from 200 trials. Pupils were not dilated. Treatment groups were 0 mg/kg ($N = 15$) and 40 mg/kg CDM ($N = 15$).

Results

For four log units of stimulus intensity, the FEPs of both groups changed considerably. In general, peak latencies decreased (Fig. 4) and peak-to-peak amplitudes increased (Fig. 5) with increasingly brighter flashes. The intensity dependence was particularly strong for the early FEP components P1 and N1. Administration of CDM increased FEP latencies independent of flash intensity. The FEP latency MANOVA had significant dose ($F(6, 23) = 9.17$, $P < 0.0001$) and intensity ($F(18,233) = 21.44$, $P < 0.0001$) main effects, but the dose × intensity interaction was nonsignificant ($F(18,233) = 1.46$, $P = 0.1043$).

The FEP amplitudes were also changed by CDM in experiment 3. Although the main effect of dose in the FEP amplitude MANOVA was not statistically significant ($F(5,24) = 1.81$, $P = 0.1499$), there was a significant intensity effect ($F(15,320) = 7.73$, $P < 0.0001$), and a significant dose × intensity interaction ($F(15,236) = 2.22$, $P = 0.0065$). The dose × intensity interaction was significant for only one peak-to-peak amplitude, P2N2 ($F(2,83) = 6.19$, $P = 0.0008$). Bonferroni-corrected t tests for the various intensity values showed that P2N2 amplitude for the CDM group approached the criterion for statistical significance only at 10^5 lx ($P = 0.0177$).

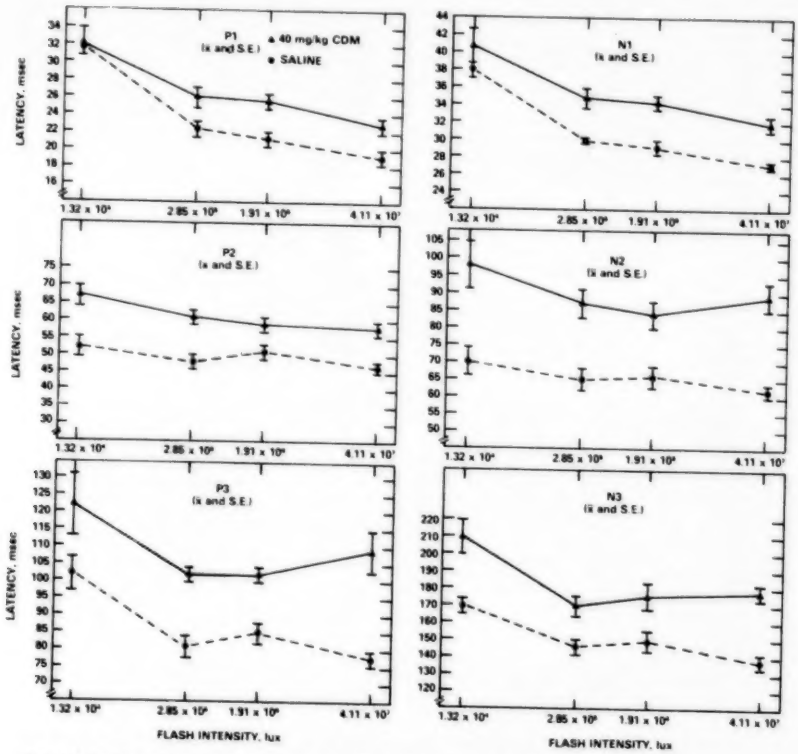


FIG. 4. Flash evoked potential (FEP) peak latencies as a function of flash intensity in rats treated with saline or CDM. Each rat received only one dose and all flash intensities in a counterbalanced order. Peak latencies, particularly the earlier components P1 and N1, decreased with increasing flash intensity. CDM treatment increased peak latencies independently of intensity.

EXPERIMENT 4

Materials and Methods

The results of experiment 1 demonstrated that when using high-contrast square-wave gratings to elicit PREPs, CDM increased the response amplitude at all but the smallest size of stimulus used (0.8 cpd). This could be due to differential CDM action on spatial-frequency selective channels. Unfortunately, the stimuli used had a square-wave spatial luminance profile which may contain visible higher frequency harmonics (11). A better test of the

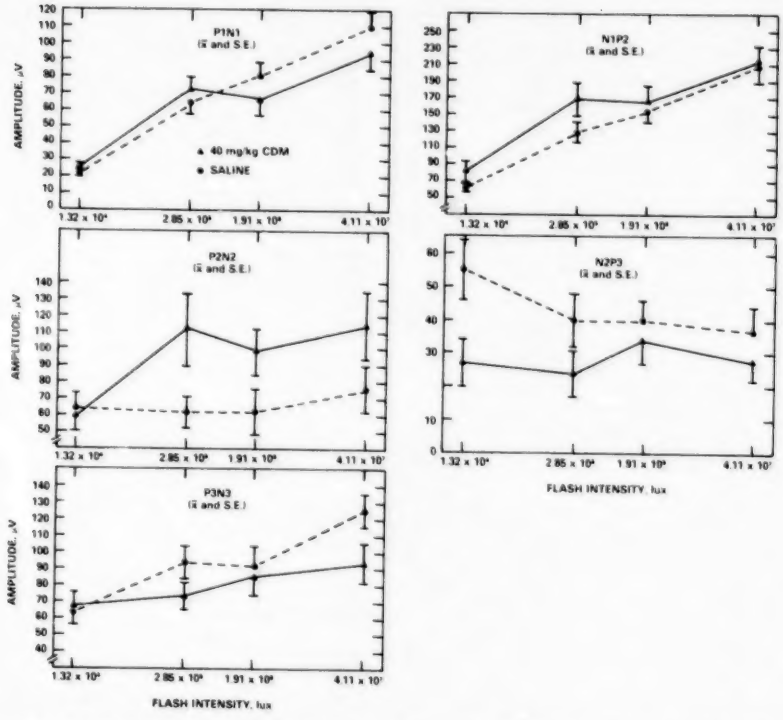


FIG. 5. FEP peak-to-peak amplitudes as a function of flash intensity in rats treated with saline or 40 mg/kg CDM. The early FEP components P1 and N1 increased monotonically with flash intensity. Peak P2N2 amplitude showed a statistically significant dose × intensity interaction.

spatial-frequency selectivity of CDM action would employ stimuli with a purely sinusoidal spatial luminance profile. Alternatively, because rats are much less sensitive to contrast at 0.8 cpd than lower spatial frequencies (1), the CDM effect may be apparent only in cases of high visibility, and be independent of spatial frequency. To address these issues, PREPs were recorded using equipment capable of generating stimuli with a sinusoidal spatial luminance profile, and of variable contrast.

The stimuli were generated with a SYM-1 microcomputer-based grating generator (Keck and Fritsch Associates, Cleveland, Ohio) and presented on a Hewlett–Packard 1317B cathode-ray tube. The display oscilloscope was operated over a brightness range for which screen illumination (calibrated

with an EG & G 450-1 radiometer/photometer) was a linear function of *z*-axis input voltage. The stimuli were vertical gratings with a sinusoidal spatial limunance profile at two spatial frequencies. At 0.2 cpd, the contrast values were 1.5, 3, 5, 10, 30, and 65%, and at 0.8 cpd 40, 50, and 65%. Rats were treated i.p. with either saline (N = 14) or 40 mg/kg CDM (N = 15) 1 h before testing. Each spatial frequency/contrast combination, and a noise condition as in experiment 1, were presented in random order. Evoked potentials were triggered with the abrupt 180-deg phase shift of the spatial gratings at 0.5 Hz. Electrocortical recordings were processed as described above with the exception that evoked potential peaks were automatically selected, with operator peak verification, using a computerized peak-selection program. Three peaks were selected and labeled N1, P1, and N3.

Results

The P1N3 peak-to-peak amplitudes of rats treated with either saline or CDM are presented as a function of stimulus spatial frequency and contrast in Fig. 6. The PREP amplitudes of both groups increased as a function of contrast at both spatial frequencies. The amplitudes for equal contrast values were considerably smaller at 0.8 than at 0.2 cpd. The effect of CDM treatment at 0.2 cpd was to increase the PREP amplitudes, but only at the high contrast values of 30 and 65%. At the lower contrast values of 1.5, 3, 5, and 10% for 0.2 cpd spatial frequency, and at all contrast values for 0.8 cpd spatial frequency, the amplitudes of the CDM group were not different from controls. Data analysis revealed that at 0.2 cpd, both the main effect of contrast (MANOVA $F(10,256) = 17.90$, $P < 0.0001$) and the dose $\times$ contrast interaction (MANOVA $F(10,252) = 2.73$, $P = 0.0033$) were statistically significant. Administration of CDM was ineffective at the higher spatial frequency. At 0.8 cpd, although there was a statistically significant effect of contrast (MANOVA $F(4,86) = 4.35$, $P = 0.0030$), there was no significant dose $\times$ contrast interaction (MANOVA $F(4,86) = 0.47$), $P = 0.7591$).

Analysis of peak latency data revealed no statistically significant effects of dose, contrast, or the dose $\times$ contrast interaction at either 0.2 or 0.8 cpd (MANOVA, all P's > 0.025; the required P value).

DISCUSSION

Exposure to CDM produced large changes in visual evoked potentials consistent with previous findings (6). In earlier studies, doses of 5, 15, and 40 mg/kg CDM produced PREP amplitude and latency increases in a dose-

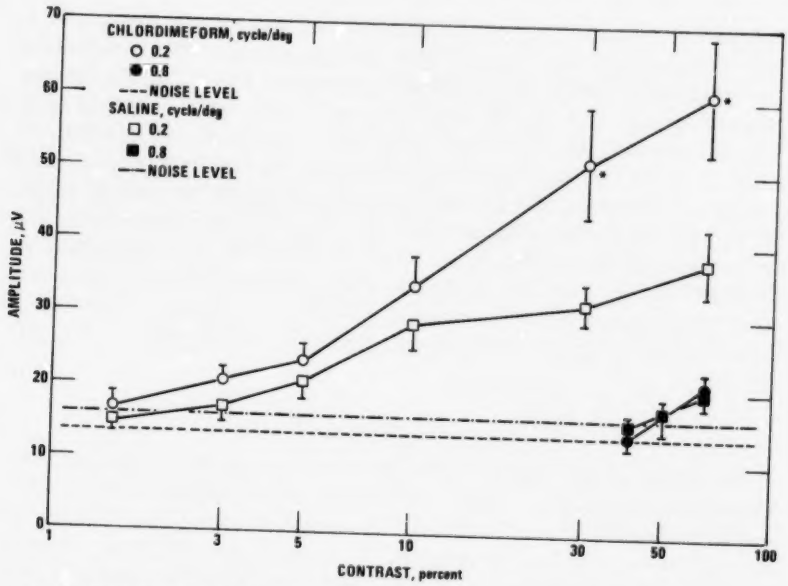


FIG. 6. PREP P1N3 peak-to-peak amplitude as a function of stimulus spatial frequency and contrast. Stimuli were vertical gratings with a sinusoidal spatial luminance profile. Administration of CDM increased the PREP amplitude only at 0.2 cpd and only at the two higher contrast values, 30 and 65%.

related fashion. The changes were transient, lasting less than 24 h. Subsequently, the peak latency changes were found to be largely secondary to CDM-induced hypothermia (8). In the current studies, the increases in PREP amplitude were dependent on stimulus primary spatial frequency when stimuli with equal contrast and a square-wave spatial luminance profile were used. Amplitude increases were large through the low and middle range tested, 0.1, 0.2, and 0.4 cpd. At the higher primary spatial frequency (0.8 cpd), CDM produced no measurable change in evoked potentials. Although 0.8 cpd is within the range of visual acuity of hooded rats [1.2 cpd (1)], only a small portion of the rat retinal ganglion cells are sensitive to stimuli as small as 0.8 cpd (15), which accounts for the relatively small size of the resulting PREPs in control rats. Onofrj *et al.* (33) reported that only 27% of their rats showed consistent PREPs at 0.5 cpd; however, they used an anesthetized preparation which gave smaller-amplitude and longer-latency responses than an awake rat preparation (5). We find that

evoked potentials, although small in amplitude, can be recorded to a 0.8 cpd stimulus.

Because the spatial frequency of 0.8 cpd is near the limit of the range of the hooded rats' contrast sensitivity function (1), stimuli at 0.8 cpd would be less visible than equal contrast stimuli at lower spatial frequencies. In experiment 1, the apparent spatial-frequency selectivity of CDM action could have resulted from either a differential sensitivity to CDM among the spatial-frequency channels, or from an enhanced susceptibility to CDM for highly visible, high "effective" contrast stimuli. Experiment 4 addressed this question by recording PREPs over a range of contrast values at 0.2 and 0.8 cpd. If, in control rats, equal amplitude PREPs can be used as an indication of equally "effective" contrast, then from Fig. 6 contrast values from 3 to 5% at 0.2 cpd were approximately equivalent to contrast values from 50 to 65% at 0.8 cpd; CDM was ineffective over this range. Administration of CDM increased PREP amplitude only above 10% contrast values at 0.2 cpd, indicating that CDM specificity of action was probably directly related to contrast, and only indirectly related to spatial frequency because of differential contrast sensitivity at different spatial frequencies. Thus, CDM apparently altered the function of visual contrast encoding mechanisms.

Bodis-Wollner and Hendley (4) found differential effects of grating adaptation on the detection of contrast differences in low- and high-contrast gratings, and proposed the existence of two contrast detection mechanisms, one for steady and one for modulated contrast. The finding that CDM selectively enhances the response to high- but not low-contrast stimuli supports the evidence for multiple-contrast encoding mechanisms. Furthermore, it demonstrates that the mechanisms are distinguishable through their response to an exogenous compound. Alternatively, Murray and Kulikowski (30) noted that a number of investigators have found two-branched functions of PREP amplitude when plotted against log stimulus contrast in monkeys and humans, with a branch point at approximately 5 to 10% contrast. Based on psychophysical evidence, they proposed that the high-contrast limb corresponds to the functioning of motion detectors and the low-contrast limb to the functioning of pattern detectors. In Fig. 6 the rat amplitude-log contrast function of the CDM-treated rats appears to have two limbs with a branch point at around 5 to 10% contrast. Although the control-rat function in Fig. 6 does not clearly contain two segments, others have found two-limbed amplitude-log contrast functions in nontreated rats (17). CDM may have selectively increased the slope of the high-contrast limb. The rat visual system contains many neurons responsive to moving stimuli (9, 41). If the rat PREP amplitude-log contrast functions are

comparable to those in monkeys and humans, then the effect of CDM could be to selectively enhance the responsiveness of motion detection mechanisms in the rat visual system.

Friedman and Green (15) reported a bimodal spatial acuity distribution of retinal ganglion cells in Long–Evans hooded rats, the lower population ranging from approximately 0.1 to 0.4 cpd with a peak around 0.3 cpd, and the higher from approximately 0.4 to 1.2 cpd with a peak around 0.8 cpd. Sensitivity to CDM was greatest to high-contrast stimuli around 0.2 cpd, and less at 0.8 cpd. It is possible that retinal ganglion cells with receptive fields responding to lower spatial frequencies are susceptible to CDM, and those with higher spatial-frequency receptive fields are not. This relationship is uncertain, however, because it is not possible to implicate one particular site of action from the results of cortical macroelectrode recordings alone. Differential spatial frequency selectivity is related to receptive field size, coded in the retina, and maintained throughout the visual system. The action of CDM could have occurred at retinal, lateral geniculate, or cortical levels. Pharmacologic distinctions between cat X and Y retinal ganglion cells have been reported (22–24). However, this alone cannot account for the CDM effect in rats because the X-like and Y-like cells do not show the spatial-frequency differential found in cats (26).

Previously, we had failed to find any CDM-induced amplitude changes in FEPs elicited from bright (10^7 lx peak power) flashes even though PREP amplitudes were greatly increased (6). When FEPs were recorded for a range of intensities (experiment 3), a significant dose $\times$ intensity interaction in peak-to-peak amplitudes was found, indicating that the CDM effects were intensity-dependent. The magnitude of the FEP changes were small, however, in comparison with the 200 to 300% increase in PREPs produced by CDM, suggesting that the difference in responsiveness to CDM between FEPs and PREPs was not due to stimulus intensity alone. Instead, because the FEP stimulus was devoid of contrast, these data provide further evidence of the contrast-dependence of CDM's action on PREPs.

The action of CDM on PREPs was independent of stimulus orientation. The neural encoding of orientation occurs largely at the level of visual cortex, although some retinal ganglion cells display orientation preferences in cats (40) and rats (21). In rats, however, only a small proportion of the cells in visual cortex have orientation-selective receptive fields (34, 39, 41). The failure of stimulus orientation to alter the CDM-induced enhancement of PREP amplitudes suggests that the means of encoding contrast and orientation are at least partially independent.

Harding *et al.* (16) found that physostigmine blocked, and atropine restored, PREPs to low spatial-frequency gratings in cats. The influence of

those agents on the response to high spatial-frequency gratings was minimal, indicating the presence of a cholinergic-sensitive channel which was tuned to low spatial frequencies. CDM also disrupted the response to low spatial-frequency stimuli, although only at high contrast. In addition, CDM enlarged PREP amplitudes whereas cholinergic agents diminished PREP amplitudes. CDM has little action on cholinergic processes (27). In insects, CDM is an agonist of octopamine, an invertebrate monoaminergic neurotransmitter (14, 20, 31). Octopamine is present in mammalian neurons, but its role as a vertebrate neurotransmitter is uncertain (37). Robinson and Bittle (38) found that CDM had partial α-adrenergic agonistic/antagonistic activity in rabbit ear arteries *in vitro*. If, as Hollingworth and Lund (19) proposed, CDM has monoaminergic activity in mammalian neurons, then monoaminergic disruption may enhance the response of a low spatial frequency, high contrast system in rats. Chlordimeform has been widely reported to be a monoamine oxidase inhibitor, but this activity does not appear to be the mechanism of visual evoked potential disruption because the monoamine oxidase inhibitor, pargyline, produced no changes similar to CDM on PREPs (7). In addition, treatment with α-methylparatyrosine, a tyrosine hydroxylase inhibitor, apomorphine, or haloperidol failed to produce large amplitude increases in rat PREPs similar to CDM, although peak latencies were increased (32). Regarding FEPs, dopamine depletion, but not norepinephrine depletion, increased the early FEP peak latencies (13). CDM also delayed FEP peaks, but the increases were probably secondary to hypothermia (8). The determination of whether the selective action of CDM on rat visual evoked potentials occurs through monoaminergic disruptions, or through some other CDM action, awaits further research.

REFERENCES

1. BIRCH, D., AND G. H. JACOBS. 1979. Spatial contrast sensitivity in albino and pigmented rats. *Vision Res.* **19**: 933–938.
2. BODIS-WOLLNER, I. 1972. Visual acuity and contrast sensitivity in patients with cerebral lesions. *Science* **17**: 769–771.
3. BODIS-WOLLNER, I., AND S. P. DIAMOND. 1976. The measurement of spatial contrast sensitivity in cases of blurred vision associated with cerebral lesions. *Brain* **99**: 695–710.
4. BODIS-WOLLNER, I., AND C. D. HENDLEY. 1979. On the separability of two mechanisms involved in the detection of grating patterns in humans. *J. Physiol. (London)* **291**: 251–263.
5. BOYES, W. K., AND R. S. DYER. 1983. Pattern reversal visual evoked potentials in awake rats. *Brain Res. Bull.* **10**: 817–823.
6. BOYES, W. K., AND R. S. DYER. 1984. Chlordimeform produces profound, selective, and transient changes in visual evoked potentials of hooded rats. *Exp. Neurol.* **86**: 434–447.

7. BOYES, W. K., V. C. MOSER, R. C. MACPHAIL, AND R. S. DYER. 1985. Monoamine oxidase inhibition cannot account for visual evoked potential changes produced by chlordimeform. *Neuropharmacology*, in press.
8. BOYES, W. K., S. PADILLA, AND R. S. DYER. 1985. Body temperature-dependent and independent actions of chlordimeform on rat visual evoked potentials and optic nerve axonal transport. *Neuropharmacology*, in press.
9. BURNE, R. A., J. G. PARNAVELAS, AND C.-S. LIN. 1984. Response properties of neurons in the visual cortex of the rat. Exp. Brain Res. **53:** 374–383.
10. CAMISA, J., L. H. MYLIN, AND I. BODIS-WOLLNER. 1981. The effect of stimulus orientation on the visual evoked potential in multiple sclerosis. *Ann. Neurol.* **10:** 532–539.
11. CAMPBELL, F. W., AND J. G. ROBSON. 1968. Application of Fourier analysis to the visibility of gratings. *J. Physiol. (London)* **197:** 551–566.
12. DYER, R. S., AND W. K. BOYES. 1983. Hypothermia and chloropent anesthesia differentially affect the flash evoked potentials of hooded rats. *Brain Res. Bull.* **10:** 825–831.
13. DYER, R. S., W. E. HOWELL, AND R. C. MACPHAIL. 1981. Dopamine depletion slows retinal transmission. *Exp. Neurol.* **71:** 326–340.
14. EVANS, P. D., AND J. D. GEE. 1980. Action of formamidine pesticides on octopamine receptors. *Nature* **287:** 60–62.
15. FRIEDMAN, L. J., AND D. G. GREEN. 1982. Ganglion cell acuity in hooded rats. *Vision Res.* **22:** 441–444.
16. HARDING, T. H., R. W. WILEY, AND A. W. KIRBY. 1983. A cholinergic-sensitive channel in the cat visual system tuned to low spatial frequencies. *Science* **221:** 1076–1078.
17. HARNOIS, C., I. BODIS-WOLLNER, AND M. ONOFRJ. 1984. The effect of contrast and spatial frequency on the visual evoked potential of the hooded rat. *Exp. Brain Res.* **57:** 1–8.
18. HIRSCH, H. V. B., AND D. N. SPINELLI. 1970. Visual experience modifies distribution of horizontally and vertically oriented receptive fields in cats. *Science* **168:** 869–871.
19. HOLLINGWORTH, R. M., AND A. E. LUND. 1982. Biological and neurotoxic effects of amidine pesticides. Pages 189–227 in J. R. COATS, Ed., *Insecticide Mode of Action.* Academic Press, New York.
20. HOLLINGWORTH, R. M., AND L. L. MURDOCK. 1980. Formamidine pesticides: octopamine-like actions in a firefly. *Science* **208:** 74–76.
21. HUGHES, A. 1980. Directional units in the rat optic nerve. *Brain Res.* **202:** 196–200.
22. IKEDA, H., AND M. J. SHEARDOWN. 1982. Acetylcholine may be an excitatory transmitter mediating visual excitation of 'transient' cells with the periphery effect in the cat retina: iontophoretic studies *in vivo*. *Neuroscience* **7:** 1299–1308.
23. KIRBY, A. W. 1979. The effect of strychnine, bicuculline, and picrotoxin on X and Y cells in the cat retina. *J. Gen. Physiol.* **74:** 71–84.
24. KIRBY, A. W., AND C. ENROTH-CUGELL. 1976. The involvement of gamma-aminobutyric acid in the organization of cat retinal ganglion cell receptive fields. A study with picrotoxin and bicuculline. *J. Gen. Physiol.* **68:** 465–484.
25. KNOWLES, C. O. 1982. Structure-activity relationships among amidine acaricides and insecticides. Pages 243–277 in J. R. COATS, Ed., *Insecticide Mode of Action.* Academic Press, New York.
26. LENNIE, P., AND V. H. PERRY. 1981. Spatial contrast sensitivity of cells in the lateral geniculate nucleus of the rat. *J. Physiol. (London)* **315:** 69–79.
27. MATSUMURA, F., AND R. W. BEEMAN. 1976. Biochemical and physiological effects of chlordimeform. *Environ. Health Perspect.* **14:** 71–82.
28. MATSUMURA, F., AND R. W. BEEMAN. 1982. Toxic and behavioral effects of chlordimeform

on the American cockroach *Periplaneta americana.* Pages 229–242 in J. R. COATS, Ed., *Insecticide Mode of Action.* Academic Press, New York.

29. MULLER, K. E., D. A. OTTO, AND V. A. BENIGNUS. 1983. Design and analysis strategies in psychophysiological research. *Psychophysiology* **20:** 212–218.
30. MURRAY, I. J., AND J. J. KULIKOWSKI. 1983. VEPs and contrast. *Vision Res.* **23:** 1741–1743.
31. NATHANSON, J. A., AND E. J. HUNNICUTT. 1981. *N*-Demethylchlordimeform: a potent partial agonist of octopamine-sensitive adenylate cyclase. *Mol. Pharmacol.* **20:** 68–75.
32. ONOFRJ, M., AND I. BODIS-WOLLNER. 1982. Dopaminergic deficiency causes delayed visual evoked potentials in rats. *Ann. Neurol.* **11:** 484–490.
33. ONOFRJ, M., I. BODIS-WOLLNER, AND P. BABAK. 1982. Pattern visual evoked potentials in the rat. *Physiol. Behav.* **28:** 227–230.
34. PARNAVELAS, J. G., R. A. BURNE, AND C.-S. LIN. 1983. Distribution and morphology of functionally identified neurons in the visual cortex of the rat. *Brain Res.* **261:** 21–29.
35. REGAN, D., R. SILVER, AND T. J. MURRAY. 1977. Visual acuity and contrast sensitivity in multiple sclerosis: hidden visual loss. *Brain* **100:** 563–579.
36. REGAN, D., J. A. WHITLOCK, T. J. MURRAY, AND K. I. BEVERLY. 1980. Orientation-specific losses of contrast sensitivity in multiple sclerosis. *Invest. Ophthalmol. Vis. Sci.* **19:** 324–328.
37. ROBERTSON, H. A. 1981. Octopamine. After a decade as a putative neuroregulator. Pages 47–73 in M. B. H. YOUDIM, W. LOVENBERG, D. F. SHARMAN, AND J. R. LAGNADO, Eds., *Essays in Neurochemistry and Neuropharmacology.* Vol. 5. Wiley, New York.
38. ROBINSON, C. P., AND I. BITTLE. 1979. Vascular effects of demethylchlordimeform, a metabolite of chlordimeform. *Pestic. Biochem. Physiol.* **11:** 46–55.
39. SHAW, C., U. YINON, AND E. AUERBACH. 1975. Receptive fields and response properties of neurons in the rat visual cortex. *Vision Res.* **15:** 203–208.
40. THIBOS, L. N., AND W. R. LEVICK. 1980. Orientation tuning curves of cat retinal ganglion cells. *Invest. Ophthalmol. Vis. Sci. Suppl.* **19:** 6.
41. WIESENFELD, Z., AND E. E. KORNEL. 1975. Receptive fields of single cells in the visual cortex of the hooded rat. *Brain Res.* **94:** 401–412.